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| 09/692,807 | 10/20/2000 | Ghazwan Saleem Butrous | PC10370A | 6255 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/692,807 | GHAZWAN SALEMM BUTROUS ET AL. | |
| | Examiner | Art Unit | |
| | Dwayne C Jones | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *the amendment of 29DEC2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,7-10 and 21-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-10 and 21-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Claims*

1. Claims 1, 7-10, and 21-112 are pending.

2. Claims 1, 7-10, and 21-112 are rejected.

### *Response to Arguments*

3. Applicants' arguments filed December 29, 2003 have been fully considered but they are not persuasive with respect to Takashi et al. and Ellis et al. Applicants present the following points. First, applicants argue that there is no motivation or suggestion that the claimed PDE V inhibitors could or should be tried in the treatment of pulmonary hypertension. Second, applicants allege that the instant claims are unobvious in view of Ellis et al. Next, applicants intimate that Ellis et al. do not relate the treatment of pulmonary hypertension to PDE V inhibition.

4. First, applicant argue that there is no motivation or suggestion that the claimed PDE V inhibitors could or should be tried in the treatment of pulmonary hypertension. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Takashi et al.,

however, do teach that the relaxation of vascular smooth muscle cell is shown to be related to increases in intracellular cGMP. Moreover, Takashi et al. teach and provide motivation to use type V phosphodiesterase inhibitors because it is known in the art the at that type V phosphodiesterase inhibitors are known to relax a variety of vascular smooth muscle cells in vitro and in vivo, (see page 372). Accordingly, the skilled artisan is clearly provided with the motivation to use any type V phosphodiesterase inhibitor for the vascular smooth muscle relaxation (vasodilation) in mammals with pulmonary hypertension, (see pages 371and 372).

5. Second, applicants allege that the instant claims are unobvious in view of Ellis et al. This allegation is unpersuasive because Ellis et al. specifically teach and provide motivation to the artisan to use PDE V inhibitors to treat pulmonary hypertension, (see page 2, 2nd full paragraph). Clearly, this provides the skilled artisan with motivation to use an inhibitor of PDE V to treat pulmonary hypertension. In addition, the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

6. Next, applicants intimate that Ellis et al. do not relate the treatment of pulmonary hypertension to PDE V inhibition. However, Ellis et al. teach that inhibitors of cGMP-

PDE clearly teach of treating hypertension and pulmonary hypertension, (see page 2). In fact, Ellis et al. refer to EP 463,756, which in turn teaches of pyrazaolopyrimidinone compounds, which clearly render the instant invention obvious. The skilled artisan would have been motivated to use sildenafil and other PDE inhibitors to treat pulmonary hypertension. Due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension, it would have been inherent that this particular compound of sildenafil is also a PDE V inhibitor. The fact that applicants have further specified a particular isozyme of this enzyme, in this case the type V isozyme of PDE, is an inherent trait or property with the administration of the compounds of Ellis et al. as well as EP 463,756. Accordingly, it would have been obvious to the skilled artisan to use the very same PDE inhibitory compounds, such as sildenafil, to treat pulmonary hypertension.

***Claim Rejections - 35 USC § 112***

7. The rejection of claims 1, 7-10, 21, 27, 44, 63-74 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of pulmonary hypertension with the PDE5 inhibitor of sildenafil, does not reasonably provide enablement for the prevention of pulmonary hypertension with the PDE5 inhibitor of sildenafil is withdrawn in response to the amendment of December 29, 2003.

8. The rejection of claims 1, 7, and 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention is withdrawn in view of the amendment of December 29, 2003.

***Claim Rejections - 35 USC § 102***

9. The rejection of claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Takahashi et al., which has a publication date of 19961997 for the instantly claimed compound entitled d) of claim 1 is withdrawn in response to the amendment of December 29, 2003.

***Claim Rejections - 35 USC § 103***

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. The rejection of claims 1 and 7-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902 possessing a publication date of December 22, 1994, especially for sildenafil and its derivatives is maintained and

repeated for both the above-stated and reasons of record. Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). This selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). In fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when $R^1$ is methyl; $R^2$ is n-propyl; $R^3$ is ethyl; $R^4$ is $SO_2NR^9R^{10}$; $R^9$ and $R^{10}$ together with the nitrogen atom to which they are attached form a 4-N($R^{12}$)-piperazinyl group; and $R^{12}$ is methyl, (see page 6, 2nd full paragraph). Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to

determine optimum amounts to get the maximum effect of the drug. Accordingly, the Ellis et al. reference renders the instantly claimed invention obvious.

13. The rejection of claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902, which has a publication date of December 22, 1994, for the instantly claimed compounds entitled c) and e) and f) of claim 1 derivatives is maintained and repeated for both the above-stated and reasons of record. Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). This selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). In fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when $R^1$ is methyl; $R^2$ is n-propyl; $R^3$ is ethyl; $R^4$ is $SO_2NR^9R^{10}$; $R^9$ and $R^{10}$ together with the nitrogen atom to which they are attached form a 4-N($R^{12}$)-piperazinyl group; and $R^{12}$ is methyl, (see page 6, 2nd full paragraph). The compounds disclosed by Ellis et al. have a structurally similar core structure with the a 1,3-diaziny –4 –keto moiety and other identical substituents on position no. 2 of the 1,3-diaznyl ring moiety. Furthermore, the physiological activities are analogous. The claims differ from the prior art by having an imidazole moiety and an indole moiety, respectively instead of the pyrazole moiety of Ellis et al. Also, Ellis et al. teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et al. teach of various modes of administration for these

compounds, inter alia, oral and parenteral administration, (see page 10). Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. In addition, one having ordinary skill in the art would have been motivated to select the claimed compound with the expectation that substitution of a heterocyclic ring moiety, such as imidazole or indole moieties, for another, namely a pyrazole moiety, would not significantly alter the analogous properties of the compound of the reference due to the close structural similarity of the compounds. For these reasons the instantly claimed compounds entitled c) and e) and f) of claim 1 are rendered obvious over Ellis et al.

14. The rejection of claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato et al. of JP 09059159 A2, which has an issue date of March 4, 1997 for the instantly claimed compound entitled d) of claim 1 is removed in response to the amendment of December 29, 2003.

15. The rejection of claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al., which has a publication date of 19961997 for the instantly claimed compound entitled d) of claim 1. Takahashi et al. teach of the administration of E4021, which is a type V phosphodiesterase inhibitor. Takahashi et al. are directed to the administration of a type V phosphodiesterase inhibitor to protect

against the development of right ventricular overload and medial thickening of pulmonary arteries in order to treat pulmonary hypertension. Moreover, the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug.

***Obviousness-type Double Patenting***

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1, 7-10, and 21-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 8 of U.S. Patent No. 5,250,534. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant invention and the prior art teach of the treating hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

18. Claims 1, 7-10, and 21-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2, and 4 of U.S. Patent No. 5,346,901. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant invention and the prior art teach of the treating hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

19. Claims 1, 7-10, and 21-112 are directed to an invention not patentably distinct from claims 1-4 of commonly assigned of U.S. Patent No. 5,250,534. Specifically, U.S. Patent No. 5,250,534 teaches of the treating hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

20. Claims 1, 7-10, and 21-112 are directed to an invention not patentably distinct from claims 1,2, and 4 of commonly assigned of U.S. Patent No. 5,346,901. Specifically, U.S. Patent No. 5,346,901 teaches of the treating hypertension with the administration of PDE inhibitor, namely the pyrazolopyrimidinone compounds of formula (I).

21. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned of U.S. Patent No. 5,250,534 and 5,346,901, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is

required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

22. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584. The official fax No. for correspondence is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should

you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
March 29, 2004